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Evaluating the impact of a national naloxone programme on ambulance attendance at overdose incidents: a controlled time–series analysis

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ABSTRACT

Background and Aims It has been suggested that distributing naloxone to people who inject drugs (PWID) will lead to fewer attendances by emergency medical services at opioid-related overdose incidents if peer administration of naloxone was perceived to have resuscitated the overdose victim successfully. This study evaluated the impact of a national naloxone programme (NNP) on ambulance attendance at opioid-related overdose incidents throughout Scotland. Specifically, we aimed to answer the following research questions: is there evidence of an association between ambulance call-outs to opioid-related overdose incidents and the cumulative number of 'take-home naloxone' (THN) kits in issue; and is there evidence of an association between ambulance call-outs to opioid-related overdose incidents in early adopter (pilot) or later adopting (non-pilot) regions and the cumulative number of THN kits issued in those areas? **Design** Controlled time–series analysis. **Setting** Scotland, UK, 2008–15. **Participants** Pre-NNP implementation period for the evaluation was defined as 1 April 2008 to 31 March 2011 and the post-implementation period as 1 April 2011 to 31 March 2015. In total, 3721 ambulance attendances at opioid-related overdose were recorded for the pre-NNP implementation period across 158 weeks (mean 23.6 attendances per week) and 5258 attendances across 212 weeks in the post-implementation period (mean 24.8 attendances per week). **Intervention** Scotland's NNP; formally implemented on 1 April 2011. **Measurements** Primary outcome measure was weekly incidence (counts) of call-outs to opioid-related overdoses at national and regional Health Board level. Data were acquired from the Scottish Ambulance Service (SAS). Models were adjusted for opioid replacement therapy using data acquired from the Information Services Division on monthly sums of all dispensed methadone and buprenorphine in the study period. Models were adjusted further for a control group: weekly incidence (counts) of call-outs to heroin-related overdose in the London Borough area acquired from the London Ambulance Service. **Findings** There was no significant association between SAS call-outs to opioid-related overdose incidents and THN kits in issue for Scotland as a whole (coefficient 0.009, 95% confidence intervals = −0.01, 0.03, $P = 0.39$). In addition, the magnitude of association between THN kits and SAS call-outs did not differ significantly between pilot and non-pilot regions (interaction test, $P = 0.62$). **Conclusions** The supply of take-home naloxone kits through a National Naloxone Programme in Scotland was not associated clearly with a decrease in ambulance attendance at opioid-related overdose incidents in the 4-year period after it was implemented in April 2011.

Keywords Ambulance, controlled time–series, evaluation, naloxone, opioid, overdose.

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INTRODUCTION

Drug-related death (DRD) is a global public health issue and a major cause of premature mortality among people who inject drugs (PWID) [1]. Opioid misuse is of particular concern and accounts for an estimated 69 000 deaths world-wide each year [2]. DRD rates in Scotland are higher than in any other UK region and are among the highest in Europe [3].

Since first proposed in 1996 [4], the distribution of the opioid antagonist naloxone for lay administration [henceforth, 'take-home naloxone (THN)'] has emerged as a key

component of DRD prevention strategies internationally. Guidelines published by the World Health Organization (WHO) in 2014 [2] recommended expansion of naloxone access to people likely to witness an overdose in their community, and it is now supplied to PWID and their family/friends in an increasing number of countries. In the United States, it is estimated that more than 26 000 peer-administered naloxone reversals (i.e. where naloxone was used to 'reverse' an opioid-related overdose) were achieved between 1996 and 2014 [5]. Following successful pilots in three regions of Scotland, the Scottish Government established a national naloxone programme (NNP) in 2010 aimed at reducing DRD rates: the first of its kind anywhere in the world [6].

Using interrupted time–series analysis, Walley *et al.* [7] compared communities in Massachusetts (USA) with high and low rates of THN implementation to those with no implementation and found evidence of a dose-related impact where higher cumulative rates of implementation were associated with greater reductions in death rates. Since its inception, the NNP in Scotland has distributed more than 20 000 THN kits, which have been associated with a 36% reduction in opioid-related deaths during the 4 weeks following prison release [8].

Despite such successes, the supply of THN remains controversial, as it is thought that it may increase risky behavior, e.g. by encouraging PWID to consume greater volumes of drugs in the knowledge that they have a 'safety net'. One additional concern is that availability of THN would lead to fewer calls to the emergency medical services if it appeared to have resuscitated the overdose victim successfully [9]. Indeed, it has been suggested that distributing THN to PWID will lead to a perception that it is a 'magic bullet' and is all that is required to reverse an overdose, negating the need for any attendance by the emergency medical services [10].

These reported concerns are not without foundation. Just fewer than two-thirds (62%) of PWIDs surveyed in San Francisco reported that they would be less likely to call emergency services if they had access to naloxone [11]. Homeless drug users in the United Kingdom have also intimated that they would see THN as an appropriate substitute to calling an ambulance at an overdose event [12]. In such a scenario, THN has the potential to create an additional barrier to PWID accessing help from professional health-care providers if they perceive that they can self-manage any opioid overdose they encounter. This is problematic, given that naloxone is short-acting and that the patient may revert into a state of overdose [13,14].

In observational studies of THN which recorded ambulance call-outs to overdose incidents at follow-up attendance ranged from 29 to 100%; two-thirds of studies reported figures of fewer than 50% [14]. Attendance by emergency medical personnel is perceived negatively by PWID due mainly to its association with police attendance [15–17]. Ambulance attendance reduces potential for rebound toxicity and provides access to professional emergency care, which those suffering an opioid-related overdose require. As well as provision of immediate clinical assessment and care, ambulance attendance at the scene of an overdose offers potential for distribution of THN to those who have been unable to access it through existing supply routes [18] or those seeking re-supply of already used kits.

Evidence for the unintended consequences of THN is currently limited. In particular, studies of the impact of naloxone supply among PWID at a population level are lacking. To address this key gap in the THN literature, this population-level ecological study aimed to evaluate the impact of a NNP on ambulance attendance at overdose. Specifically, we aimed to answer the following research questions:

1 Is there evidence of an association between ambulance call-outs to opioid-related overdose incidents and the cumulative number of THN kits in issue as adjusted for opioid replacement therapy (ORT) and a control group?
2 Is there evidence of an association between ambulance call-outs to opioid-related overdose incidents in early adopter (pilot) areas and the cumulative number of THN kits issued in those areas as adjusted for ORT and a control group?
3 Is there evidence of an association between ambulance call-outs to opioid-related overdose incidents in later adopting (non-pilot) areas and the cumulative number of THN kits issued in those areas as adjusted for ORT and a control group?

The current study is timely, given the increasing adoption of THN internationally, the importance of ambulance attendance at opioid-related overdose and uncertainty about the effect of THN on such attendance.

METHODS

Setting

This study was conducted in Scotland, UK, 2008–15.

Intervention

The number of THN kits were supplied through Scotland's NNP, formally implemented on 1 April 2011. In Scotland, THN is supplied following a brief 5–10-minute training session, mainly via community addiction treatment and harm reduction services, and to at-risk prisoners on release. Training sessions typically cover signs and symptoms of opioid overdose, basic life support, naloxone administration and calling an ambulance.

Observations

The pre-NNP implementation period for the evaluation was defined as 1 April 2008 to 31 March 2011 and the post-implementation period as 1 April 2011 to 31 March 2015. In total, 3721 ambulance attendances at opioid-related overdose were recorded for the pre-NNP implementation period across 158 weeks (mean 23.6 attendances per week) and 5258 attendances across 212 weeks in the post-implementation period (mean 24.8 attendances per week).

Primary outcome measure

Weekly Scottish Ambulance Service (SAS) call-out counts to opioid-related overdoses.

Design

Overview

Time–series analysis was undertaken for the period 1 April 2008 to 31 March 2015 using weekly call-outs to opioid-related overdose by the SAS as the dependent variable and cumulative number of THN kits issued as part of the NNP as the explanatory variable. Pre-NNP implementation period for the evaluation was defined as 1 April 2008 to 31 March 2011 and the post-implementation period as 1 April 2011 to 31 March 2015. Roll-out of the programme was not uniform across the country from 1 April 2011 (see Appendix S1), therefore we used the number of cumulative kits in issue as a continuous covariate within the model rather than a single date of implementation. Analysis was adjusted for ORT, and London ambulance call-outs to heroin overdoses were included as a control. Supplementary analysis was undertaken to explore whether effects varied between early adopters (i.e. the three pilot regions) and those engaging with the programme at a later date. All analysis was pre-specified in an analysis plan.

Data

Anonymized data were obtained on all weekly THN supplies provided for lay administration in Scotland through the NNP between 2011 and 2015. Given the focus of the study on lay administration, only supplies made to those at risk of opioid overdose and their family/friends were included; supplies made to service staff were excluded. Data on THN kits supplied were provided by the Information Services Division of the National Health Service Scotland at both national and regional levels. Data on THN kits supplied in Scotland before this period (e.g. within the three early adopting regions during their pilot phase) were not included within the study due to inconsistencies in data collection methods across the three regions.

Anonymized data were also requested on all ambulance attendances at opioid-related overdose incidents between 2008 and 2015. Data were drawn from the final Advanced Medical Priority Dispatch System codes input by the ambulance crew who had seen the patient face-to-face. Based on advice from SAS colleagues, we included incidents where diagnostic code 23C05 [Overdose/Poisoning, Narcotics (Heroin)] was used or where diagnostic code group 23 (Overdose/Poisoning) was used and the additional factor 'opiate' was noted by the crew. Data were again supplied on a weekly basis at both national and regional levels. SAS attendance data are limited in terms of details which would allow analysis of subgroups. The only additional data available beyond the date of the incident and type of overdose involved were postcodes (four-digit). In light of these data limitations we elected to explore potential differential impacts by regional area only within supplementary analysis.

Despite establishing contact with representatives from other administrations, no suitable control area was identified. This was either as a result of absence of data (England, Ireland, Northern Ireland) or because of the existence of another NNP (Wales). During this scoping exercise we identified ambulance attendance data for the London Borough area, specifically London Ambulance Service (LAS) attendance at 'heroin-related' overdose. As in Scotland, LAS data were also drawn from the dispatch code for overdose, but specifically for cases where 'heroin' was noted. As well as being based on the term 'heroin' only, these data differed from those provided by SAS in that they were derived from the system used by the call-handlers within the ambulance control centre (not the 'final' dispatch code sourced from the ambulance crew clinical notes as used within the SAS data). No other data on opioid-related overdose were available from LAS.

Potential confounding variables were considered and decided upon based on evaluating the existing literature and availability of data. To be included, confounders had to link plausibly to both the outcome and exposure and be time-variant (i.e. weekly or monthly). For example, ORT was included given the established evidence that drug treatment is protective against overdose [19] and also that treatment services are one of the main vehicles in the community for supplying THN within the NNP. Therefore, anonymized data on the total sum of all prescribed quantities [dispensed in milligrams (mg)] of methadone and buprenorphine between 2008 and 2015 were sourced from the Information Services Division, this time on a monthly basis (weekly not available) at national and regional levels. Both ORT measures were included separately because it was not possible to combine them into a single meaningful measure due to dose discrepancy.

Statistical analysis

SAS call-out counts for opioid-related overdoses are time–series data and likely to be autocorrelated, therefore standard regression techniques are unsuitable. One approach to modelling time–series data is to use regression models with autoregressive integrated moving average (ARIMA) errors. The first step in the modelling strategy was to inspect autocorrelation and partial autocorrelation plots of the dependent variable (i.e. the weekly ambulance call-out counts) in order to determine the underlying error structure of the models [20]. Error terms were added to reduce autocorrelation then removed systematically to find the most parsimonious model. The preferred model was then subjected to standard diagnostic tests including checking for autoregressive conditional heteroscedasticity (ARCH effects) [21] by comparing standard errors produced with and without the robust option and checking that residuals contained no remaining autocorrelation. The explanatory variable (cumulative THN kits) was then added to this initial model before testing the effect of the additional covariates (ORT—methadone and buprenorphine) and the LAS call-out data [22]. The SAS call-out data were log-transformed to stabilize the variance in the series. Goodness-of-fit is reported as R^2 between observed and fitted models. The Bayes factor was calculated for the results of the main analysis [23]. To test whether the effect size was different in the pilot compared to the non-pilot regions, an interaction term between a variable indicating pilot/non-pilot and the cumulative THN kits was added to the modelling [linear regression with lag terms identified by the time–series modelling was used for this purpose as data were no longer a single time–series with two observations per time-point (from pilot and non-pilot regions)].

All analyses were undertaken using Stata/SE 14 software (Stata Corp, College Station, TX, USA, 2015). Graphs were produced in R version 3.2.0 (R Development Core team, Vienna, Austria, 2008). Ethical approval was not required for this study.

RESULTS

Descriptive analysis

Figure 1 shows crude trends in weekly incidence of SAS call-outs to opioid-related overdoses. Figure 2 shows crude trends in weekly supplies of THN, LAS call-outs to heroin-related overdoses and monthly ORT prescription data (methadone and buprenorphine). The implementation date when THN kits began to be made available to PWID is marked by a vertical line on each figure at 1 April 2011.

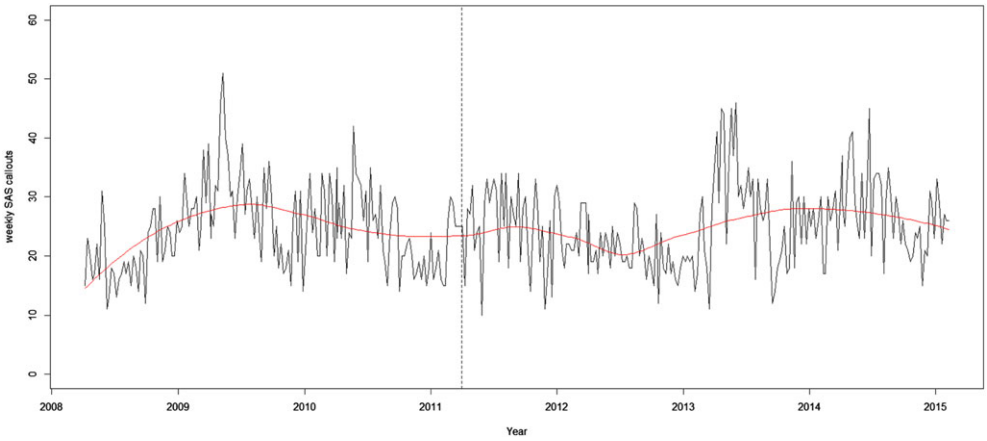
Visual inspection of the data shows that opioid-related SAS call-outs did not appear to reduce after THN kits started to be issued (Fig. 1). The mean weekly number of SAS call-outs to opioid-related overdose over the period of the study increased from 23.6 in the pre-NNP era (2008–11) to 24.8 in the 4-year period following implementation (2011–15). Seasonal variation is evident with summer peaks visible across the majority of the time–series. LAS call-outs to heroin-related overdoses also appeared to increase in the post-April 2011 period with the mean weekly number increasing from 2.9 (2008–11) to 5.1 (2011–15) across the time–series (Fig. 2).

For ORT, methadone prescriptions were on an increasing trend between 2008 and 2011, but appeared to peak around April 2011 then reduce thereafter. In contrast, buprenorphine prescriptions increased steadily over the period under review.

Statistical analysis

Main model

There was no evidence that the number of THN kits in issue was associated with a difference in SAS call-outs to



[1] Red-line represents use of LOESS to apply a smooth non-linear curve to the time-series based on 40% of the data points

Figure 1 Weekly call-outs to opioid-related overdose (Scottish Ambulance Service), 2008–15 [1]

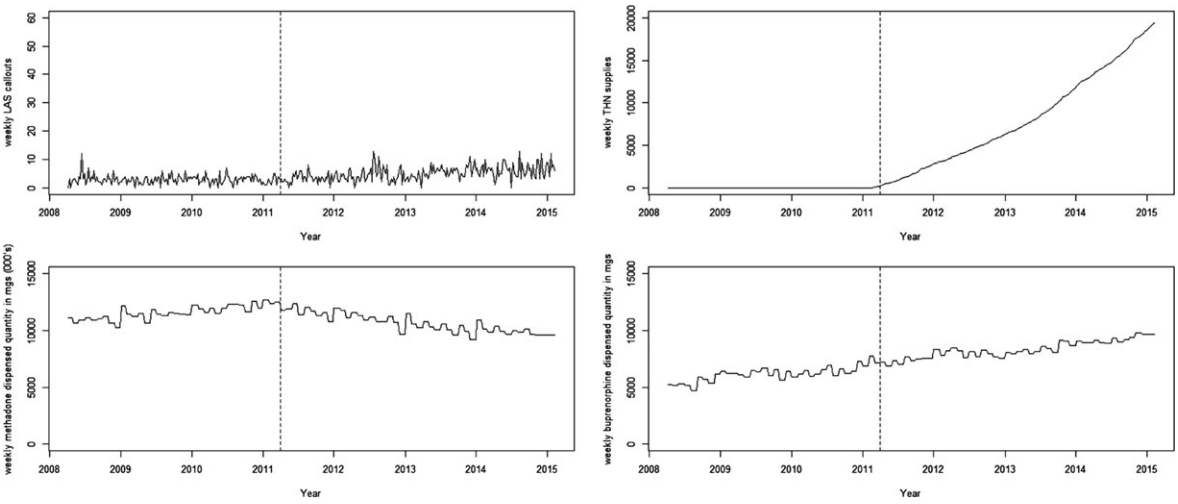


Figure 2 Weekly call-outs to heroin-related overdose (London Ambulance Service), 2008–15; weekly supplies of take-home naloxone (THN) made via the Scottish national naloxone programme (NNP), by setting, 2008–15; monthly prescribed quantities of methadone (dispensed in mg), Scotland, 2008–15; monthly prescribed quantities of buprenorphine (dispensed in mg), Scotland, 2008–15

opioid-related overdoses. For Scotland as a whole, the coefficient relating to each of the 1000 THN kits in issue (adjusted for ORT and London ambulance control) was 0.009 [95% confidence interval (CI) = −0.01 to 0.03, $P = 0.39$] (Table 1). The Bayes factor was calculated as 9.58, which can be interpreted to mean that the null hypothesis (i.e. that THN was not associated with SAS call-outs) is almost 10 times more likely to be true than the alternative hypothesis (i.e. that THN was associated with SAS call-outs).

Supplementary analysis

In the three early adopter (pilot) regions there was no evidence that the number of THN kits in issue was associated with weekly SAS call-outs (coefficient 0.059, 95% CI = −0.03 to 0.16, $P = 0.22$) (Table 1). In the later adopting (non-pilot) regions there was no evidence that the number of THN kits in issue was associated with a difference in weekly SAS call-outs (coefficient − 0.024, 95% CI = −0.08 to 0.04, $P = 0.42$) (Table 1). The *P*-value from the interaction test was 0.62, indicating no evidence of a different magnitude of association between THN kits and SAS call-outs in pilot and non-pilot regions.

DISCUSSION

Contrary to prior speculation in the literature, our results show that supply of THN through an NNP in Scotland has not been associated with a decrease in ambulance attendance at opioid-related overdose incidents in the 4-year period after it was introduced. These findings were consistent in both national level analysis and when

Table 1 weekly change in Scottish Ambulance Service call-outs to opioid-related overdoses per 1000 kits in issue.

		Effect per 1000 kits	*SE per 1000 kits*	*95 % CIs*		*P-value R-squared*	
				Lower	*Upper*		*%*
All areas	Unadjusted	0.001	0.006	0.00	0.02	0.23	27.4
	Adjusted for ORT	0.001	0.011	−0.01	0.03	0.29	28.1
	Adjusted for ORT with London control	0.009	0.011	−0.01	0.03	0.39	28.3
Pilot areas	Unadjusted	0.043	0.034	−0.02	0.11	0.20	18.9
	Adjusted for ORT	0.053	0.047	−0.04	0.15	0.26	19.4
	Adjusted for ORT with London control	0.059	0.047	−0.03	0.16	0.22	19.6
Non-pilot areas	Unadjusted	0.010	0.016	−0.02	0.04	0.51	18.2
	Adjusted for ORT	−0.020	0.030	−0.07	0.04	0.50	19.1
	Adjusted for ORT with London control	−0.024	0.030	−0.08	0.04	0.42	19.3

SE = standard error; CI = confidence interval; ORT = opioid replacement therapy.

exploring differences between early adopting regions and those areas implementing THN at a later date.

The main strengths of this study are in its novel use of routine data to explore potential unintended consequences associated with a NNP through controlled time–series analysis. Scotland is one of only two countries currently with a NNP (Wales being the other) and benefits from access to large national data sets collected consistently over the periods before and after implementation, thus facilitating a study of this kind. The length of the time–series is particularly important in countering spurious trends associated with overdoses occurring in clusters [7].

Despite these study strengths, the process for identifying accurately all ambulance attendances at opioid-related overdose incidents was challenging, and is prone to underestimation. Indeed, the differences in magnitude between SAS and LAS weekly call-outs are probably explained by the different data recording and coding procedures operated between the two services. However, by using the final dispatch code recorded by the SAS crew themselves, the risk of misintepretation or missing data is minimized in the main model and provides us with the best means to assess patterns in attendance accurately over time. Seasonal trends evident within the descriptive analysis validate these data further, notably the peaks in SAS attendance at opioid-related overdose in the summer months, which are consistent with previous studies [24,25]. The summer peaks are less evident in 2011 and 2012, which we ascribe to the European heroin drought during that period [26,27] and the association between heroin droughts and reductions in rates of overdose [28,29].

The threat of unmeasured confounding is particularly acute for natural experimental studies [30]. Where genuine alternative explanations for an observed effect rather than the intervention exist, internal validity may be compromised. Importantly, SAS clinical guidelines for naloxone use had not changed during the study period and were therefore unlikely to have influenced practice. The potential for alternative explanations to changes in SAS attendance at opioid-related overdose was addressed by consideration of a range of confounding variables. Although we included one confounder (i.e. ORT), others were excluded; specifically, heroin purity levels and the prison population. The former was rejected due to limited availability of relevant data and inconclusive evidence associating heroin purity levels with overdose rates [31]. The latter is linked more strongly to the outcome, given the high prevalence of illicit drug use on admission to prison, the use of prisons as a vehicle for THN supply in Scotland alongside community services and the heightened risk of overdose on release [32]. An additional factor here is the high volume of prisoners serving short-term sentences for drug and drug-related offences, which increases the incident number of transient risk periods for drug-related harms (i.e. overdose) experienced by this marginalized cohort. However, it is important to recognize that prisoners-on-release can benefit from THN kits issued from the prison estate as well as from the community, and vice versa [33]. Despite these theoretical links, time–series data on prison admissions and/or liberations were unavailable, thus the potential for residual and temporal confounding remains. Finally, we acknowledge that a potential increase (or decrease) in opioid-related deaths might have had an impact upon ambulance attendance at opioid-related overdose. However, national statistics reveal that the crude number of opioid-related deaths did not change significantly during the study period, averaging 424 in the pre-NNP era (2008–10) and 415 post-NNP implementation (2011–14) [34].

Our study would have benefited from comparison with a national 'control' area using similar data collection methods. However, insufficient data were available to progress such an approach. As an alternative we included data on heroin-related overdoses attended by LAS. This is likely to be a weak control due to the differences in data collection cited in our Methods section. Moreover, we were unable to source any available relevant data which could be used to compare the opioid markets directly (e.g. ORT prescribing data) in Scotland and London Borough. This limits further the effectiveness of LAS data as a control for opioid-related overdoses attended by SAS.

There are no specific studies, to date, which have evaluated the impact of naloxone programmes on ambulance attendance at overdose incidents. Our study provides the first empirical evidence in response to conjecture that provision of THN would lead to fewer ambulances attending opioid-related overdoses. Our results provide no evidence of such a relationship in Scotland. In reviewing the literature, we identified one previous study which investigated the impact of another key drug policy (Supervised Injecting Facility) on ambulance call-outs to overdose [35]. The authors found that the ambulance service attended significantly fewer opioid-related overdoses in the area surrounding the facility after it began operating when compared to the rest of the state of New South Wales, Australia. The effect was particularly strong during opening hours and in the immediate area surrounding the facility.

This study adds considerably to the evidence base in this field by shedding light upon one measurable example of a range of potential behavioural changes that might have occurred among those supplied with THN, and suggests that THN kits in issue are not associated with ambulance attendance at opioid-related overdose incidents. Although it is encouraging that ambulance attendance has not decreased since the introduction of NNP, nor has it increased to any substantial degree. Calling an ambulance is a core component of the Scottish NNP training model alongside overdose identification, basic life support

and naloxone administration. Opioid overdose is an acute medical condition which requires specialist intervention and support, therefore these findings should be used as a catalyst for policy and practice to reinforce the importance of calling an ambulance at all future incidents. Specifically, education and health promotion centred on calling an ambulance should be an essential element of any THN programme internationally.

As the first study of its kind, the generalizability of its findings is limited. Future research should consider the applicability of these findings over a longer time–series and in other territories to determine whether ambulance attendance at overdose events is influenced by THN in different ways across different populations. Comparison between pilot and non-pilot regions merit further exploration, in particular to determine if patterns of ambulance attendance at opioid-related overdose vary over time between early adopters and those implementing THN at a later date.

CONCLUSIONS

Our study found no evidence that the number of THN kits in issue is associated with a difference in ambulance attendance at opioid-related overdose. This study provides observational evidence to refute claims that availability of naloxone decreases incidence of ambulance attendance at overdose. Future research should consider the applicability of these findings in other territories and whether the relationship between naloxone supply and ambulance attendance at overdose is sustained in the long term.

Declaration of interests

This study was funded by NHS Health Scotland. The opinions expressed in this paper as those of the authors alone and are not necessarily those of NHS Health Scotland. The funders had no role in the conduct of the research. A.M., L.B. and C.H. served on Scotland's National Naloxone Advisory Group, but write in a personal capacity.

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References

1. Darke S., Degenhardt L., Mattick R. *Mortality Amongst Illicit Drug Users: Epidemiology, Causes and Intervention*. Cambridge: Cambridge University Press; 2006.
2. World Health Organization (WHO). *Community management of opioid overdose*. Geneva: WHO; 2014. Available at: http://www.who.int/substance_abuse/publications/management_opioid_overdose/en/ (accessed 2 February 2015) (Archived at http://www.webcitation.org/6l24psk2Y on 5 October 2016).
3. Davies C., English L., Stewart C., McVeigh J., Bellis M. A. United Kingdom Drug Situation: Annual Report to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). UK Focal Point: 31 October 2012. Available at: http://www.nta.nhs.uk/uploads/2012.pdf (accessed 2 February 2015) (Archived at http://www.webcitation.org/6l24wnW1f on 5 October 2016).
4. Strang J., Darke S., Hall W., Farrell M., Ali R. Heroin overdose: the case for take-home naloxone. *BMJ* 1996; **312**: 1435–6.
5. Centers for Disease Control and Prevention. Opioid overdose prevention programs providing naloxone to laypersons—United States, 2014. Morb Mort Wkly Rep 2015. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6423a2.htm?s_cid=mm6423a2_w (accessed 20 June 2015) (Archived at http://www.webcitation.org/6l23r9qPS on 5 October 2016).
6. McAuley A., Best D., Taylor A., Hunter C., Robertson R. From evidence to policy: the Scottish national naloxone programme. *Drug Educ Prev Policy* 2012; **19**: 309–19.
7. Walley A. Y., Xuan Z., Hackman H. H., Quinn E., Doe-Simkins M., Sorensen-Alawad A. *et al.* Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis. *BMJ* 2013; **346**: f174.
8. Bird S., McAuley A., Perry S., Hunter S. Effectiveness of Scotland's National Naloxone Programme for reducing opioid-related deaths: a before (2006–10) versus after (2011–13) comparison. *Addiction* 2015; **111**: 883–91.
9. Ashworth A. J. Emergency naloxone for heroin overdose: beware of naloxone's other characteristics. *BMJ* 2006; **333**: 754.
10. Lenton S., Hargreaves K. A trial of naloxone for peer administration has merit, but will the lawyers let it happen? *Drug Alcohol Rev* 2000; **19**: 365–9.
11. Seal K. H., Downing M., Kral A. H., Singleton-Banks S., Hammond J. P., Lorvick J. *et al.* Attitudes about prescribing take-home naloxone to injection drug users for the management of heroin overdose: a survey of street-recruited injectors in the San Francisco Bay Area. *J Urban Health* 2003; **80**: 191–301.
12. Wright N., Oldham N., Francis K., Jones L. Homeless drug users' awareness and risk perception of peer 'Take Home Naloxone' use—a qualitative study. *Subst Abuse Treat Prev Policy* 2006; **1**: 28.
13. Sporer K. Strategies for preventing heroin overdose. *BMJ* 2003; **326**: 442–4.
14. Clark A. K., Wilder C. M., Winstanley E. L. A systematic review of community opioid overdose prevention and naloxone distribution programs. *J Addict Med* 2014; **8**: 153–63.
15. Shermann S., Gann D. S., Scott G., Carlberg S., Bigg D., Heimer R. A qualitative study of overdose responses among Chicago IDUs. *Harm Reduct J* 2008; **5**: 2.
16. Lankenau S., Wagner K. D., Silva K., Kecojevic A., Iverson E., McNeely M. *et al.* Injection drug users trained by overdose prevention programs: responses to witnessed overdoses. *J Community Health* 2013; **38**: 133–41.
17. Bennett A. S., Bell A., Tomedi L., Hulsey E. G., Kral A. H. Characteristics of an overdose prevention, response, and

naloxone distribution program in Pittsburgh and Allegheny County, Pennsylvania. *J Urban Health* 2011; **88**: 1020–30.
18. Moore C., Lloyd G., Oretti R., Russell I., Snooks H. Paramedic supplied 'Take Home' naloxone: protocol for cluster randomised feasibility study. *BMJ Open* 2014; **4**: e004712.
19. Davoli M., Bargagli A. M., Perucci C. A., Schifano P., Belleudi V., Hickman M. *et al.* for the VEdeTTE Study Group. Risk of fatal overdose during and after specialist drug treatment: the VEdeTTE study, a national multi-site prospective cohort study. *Addiction* 2007; **102**: 1954–9.
20. Box G. E. P., Jenkins G. M., Reinsel G. C. *Time Series Analysis: Forecasting and Control*, 4th edn. Hoboken, NJ: Wiley; 2008.
21. Becketti S. *Introduction To Time Series Using Stata*. College Station, TX: Stata Press; 2013.
22. McCain L., McCleary M. The statistical analysis of the simple interrupted time series quasi-experiment. In: Cook T., Campbell D., editors. *Quasi-Experimentation: Design and Analysis Issues For Field Settings*. Chicago: Rand McNally; 1979, pp. 233–93.
23. Jarosz A. F., Wiley J. What are the odds? A practical guide to computing and reporting Bayes factors. *J Problem Solving* 2014; **7**: 2.
24. Knowlton A., Weir B. W., Hazzard F., Olsen Y., McWilliams J., Fields J. *et al.* EMS runs for suspected opioid overdose: implications for surveillance and prevention. *Prehosp Emerg Care* 2013; **17**: 317–29.
25. Merchant R. C., Schwartzapfel B. L., Wolf F. A., Li W., Carlson L., Rich J. D. Demographic, geographic, and temporal patterns of ambulance runs for suspected opiate overdose in Rhode Island, 1997–2002. *Subst Use Misuse* 2006; **41**: 1209–26.
26. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). 2011 Annual Report on the State of the Drugs Problem in Europe. Lisbon: EMCDDA; 2011. Available at: http://www.emcdda.europa.eu/online/annual-report/2011 (accessed 25 November 2014) (Archived at http://www.webcitation.org/6l24BVmWe on 5 October 2016).
27. Ahmad M., Richardson A. Impact of the Reduction in Heroin Supply Between 2010 and 2011: Research Report 91. London: Home Office: 2016. Available at: www.gov.uk/government/uploads/system/uploads/attachment_data/file/494423/horr91-reduction-heroin-supply.pdf (accessed 2 February 2016) (Archived at http://www.webcitation.org/6l24LQPaG on 5 October 2016).
28. Longo M. C., Henry-Edwards S. M., Humeniuk R. E., Christie P., Ali R. L. Impact of the heroin 'drought' on patterns of drug use and drug-related harms. *Drug Alcohol Rev* 2004; **23**: 143–50.
29. Weatherburn D., Jones C., Freeman K., Makkai T. Supply control and harm reduction: lessons from the Australian heroin 'drought'. *Addiction* 2003; **98**: 83–91.
30. Craig P., Cooper C., Gunnell D., Haw S., Lawson K., Macintyre S. *et al.* Using natural experiments to evaluate population health interventions: new Medical Research Council guidance. *J Epidemiol Community Health* 2012; **66**: 1182–6.
31. Darke S., Farrell M. Would legalizing illicit opioids reduce overdose fatalities? Implications from a natural experiment. *Addiction* 2014; **109**: 1237–42.
32. Merrall E. L. C., Kariminia A., Binswanger I. A., Hobbs M., Farrell M., Marsden J. *et al.* Meta-analysis of drug-related deaths soon after release from prison. *Addiction* 2010; **105**: 1545–54.
33. McAuley A., Munro A., Bird S., Hutchinson S., Goldberg D., Taylor A. Engagement in a National Naloxone Programme among people who inject drugs. *Drug Alcohol Depend* 2016; **162**: 236–40.
34. National Records of Scotland, 2014. Drug-Related Deaths in Scotland in 2014. National Records of Scotland, Edinburgh: 25 August 2015. Available at: http://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths/drug-related-deaths-in-scotland/2014 (accessed 26 August 2015) (Archived at http://www.webcitation.org/6l24Qox2v on 5 October 2016).
35. Salmon A. M., Van Beek I., Amin J., Kaldor J., Maher L. The impact of a supervised injecting facility on ambulance call-outs in Sydney, Australia. *Addiction* 2010; **105**: 676–83.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1 Scottish take-home naloxone pilot areas, their characteristics and roll-out dates.

